accompanying text in the specification (see footnotes 1-2 and accompanying text). [1,2,] Additional support can be found throughout the specification.

Claim 20 has also been amended to specifically indicates that the cardiac tissue is transfected or transduced with recombinant nucleic acid vectors that are expressed in the cardiac tissue. Support for a delivery means for delivering and transfecting or transducing a therapeutically effective amount of said recombinant nucleic acid vectors from said reservoir means through said distal tip portion of said catheter to said cardiac tissue "such that said cardiac tissue is transfected or transduced with said recombinant nucleic acid vectors"[3,4] and "said vectors are

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[1] **Starting at page 12, line 6 of the specification: At the proximal end of the catheter**, a fitting 46 is located, to which a Luer lock 48 is coupled. Luer lock 48 is coupled to the proximal end of elongated catheter body 40 and receives the lumen. A swivel mount 50 is mounted to Luer lock 48, allowing rotation of the catheter relative to Luer lock 52. Luer lock 52 in turn, is coupled through control element 54 to a tube 58 which communicates with **reservoir 55**, suitably through flow control 57 and filter 56. Reservoir 55 holds a supply of the selected genetic material **[emphasis added]**.

[2] **Starting at page 17, line 8 of the specification:** In another embodiment, as illustrated in Figure 6B, a **chamber 99 is provided just proximal from eluting electrode** 97, and serves as the **reservoir** of the genetic material. Insulating material 96 is formed from a self-sealing material such that it may be pierced with a needle, or the like, and reseal itself, thus allowing introduction of the genetic material into the chamber prior to implantation **[emphasis added]**

[3] **Starting at page 5, line 4 of the specification:** Direct transfer of genetic material into myocardial tissue in vivo has recently been demonstrated to be an effective method of expressing a desired protein. For example, direct **myocardial transfection**. of plasmid DNA by direct injection into the heart of rabbits and pigs (Gal, et al., Lab. Invest., 1993, 68, 18-25), as well as of rats (Ascadi, et al., The New Biol., 1991, 3, 71-81), has been shown to result in expression of particular reporter gene products. In addition, direct in vivo **gene transfer into myocardial cells** has also been accomplished by directly injecting adenoviral vectors into the myocardium. French, et al., Circulation, 1994, 90, 2415-2424, and PCT Publication WO 94/11506. It has long been desired to effectively treat conduction pathway abnormalities. **[emphasis added]**

[4] **Starting at page 20, line 16 of the specification:** Genetic material can be introduced into a cell or "contacted" by a cell by, for example, **transfection or transduction** procedures. Transfection refers to the acquisition by a cell of new genetic material by incorporation of added nucleic acid molecules. **Transfection** can occur by physical or chemical methods. Many transfection techniques are known to those of ordinary skill in the art including: calcium phosphate DNA co-precipitation; DEAE-dextran DNA transfection; electroporation; naked plasmid adsorption, and cationic liposome-mediated transfection. **Transduction** refers to the process of transferring nucleic acid into a cell using a DNA or RNA virus. Suitable viral vectors for use as transducing agents include, but are not limited to, retroviral vectors, adeno associated viral vectors, vaccinia viruses, and Semliki Forest virus vectors. **[emphasis added]**

Treatment of cells, or contacting cells, with recombinant nucleic acid molecules can take place in vivo or ex vivo. For ex vivo treatment, cells are isolated from an animal (preferably a human), transformed (i.e., **transduced or**

expressed in the cardiac tissue" can be found in the specification[5],[6] (see footnotes 3-4, and 5-6 for accompanying text). Additional support can be found throughout the specification.

II. RESPONSE TO THE REJECTIONS MADE IN THE FINAL OFFICE ACTION

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transfected in vitro) with a delivery vehicle containing a nucleic acid molecule encoding a conduction protein, and then administered to a recipient. Procedures for removing cells from mammals are well known to those of ordinary skill in the art. In addition to cells, tissue or the whole or parts of organs may be removed, treated ex vivo and then returned to the patient. Thus, cells, tissue or organs may be cultured, bathed, perfused and the like, under conditions for introducing the recombinant nucleic acid molecules of the invention into the desired cells. **[emphasis added]**

For in vivo treatment, cells of an animal, preferably a mammal and most preferably a human, are **transformed** in vivo with a recombinant nucleic acid molecule of the invention. The in vivo treatment may involve systemic intravenous treatment with a recombinant nucleic acid molecule, local internal treatment with a recombinant nucleic acid molecule, such as by localized perfusion or topical treatment, and the like. When performing in vivo administration of the recombinant nucleic acid molecule, the preferred delivery vehicles are based on noncytopathic eukaryotic viruses in which nonessential or complimentable genes have been replaced with the nucleic acid sequence of interest. Such noncytopathic viruses include retroviruses, the life cycle of which involves reverse transcription of genomic viral RNA into DNA with subsequent proviral integration into host cellular DNA. Retroviruses have recently been approved for human gene therapy trials. Most useful are those retroviruses that are replication-deficient (i.e., capable of directing synthesis of the desired proteins, but incapable of manufacturing an infectious particle). Such genetically altered retroviral expression vectors have general utility for high-efficiency **transduction** of genes in vivo. Standard protocols for producing replication-deficient retroviruses (including the steps of incorporation of exogenous genetic material into a plasmid, transfection of a packaging cell line with plasmid, production of recombinant retroviruses by the packaging cell line, collection of viral particles from tissue culture media, and infection of the target cells with viral particles) are provided in Kriegler, M. "Gene Transfer and Expression, a Laboratory Manual", W.H. Freeman Co., New York (1990) and Murry, E.J. e.d. "Methods in Molecular Biology", Vol. 7, Humana Press, Inc., Cliffton, New Jersey (1991). **[emphasis added]**

A preferred virus for contacting cells in certain applications, such as in vivo applications, is the adenoassociated virus, a double-stranded DNA virus. The adenoassociated virus can be engineered to be replication deficient and is capable of infecting a wide range of cell types and species. It further has advantages such as heat and lipid solvent stability, high **transduction** frequencies in cells of diverse lineages, including hemopoetic cells, and lack of superinfection inhibition thus allowing multiple series of transductions. Recent reports indicate that the adeno-associated virus can also function in an extrachromosomal fashion. **[emphasis added]**

[5] **Starting at page 6, line 2 of the specification:** In accordance with the above, the primary purpose of Applicants' claimed invention is to provide delivery systems for treating cardiac conduction disturbances. Upon identifying a problematic area within the heart, conduction protein genetic material is selected such that **expression of a selected conduction protein** corrects or improves the cardiac conduction of the cells in the problematic area. Alternatively, expression of a selected conduction protein can improve the cardiac conduction of normal, healthy cells surrounding the problematic cells. **[emphasis added]**

[6] **Starting at page 5, line 9 of the specification:** Once the specific problem has been identified, conduction protein genetic material is selected such that **expression of a selected conduction protein** corrects or improves the cardiac

In the last communication from the Examiner, the Examiner indicated that Claim 20 was rejected under 35 U.S.C. Section 112, second paragraph, for being indefinite as written. Applicants' response and amendments are submitted to overcome this rejection.

Claims 20 was newly rejected under 35 U.S.C. Section 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which Applicants regard as the invention. Claim 20 was considered confusing such that metes and bounds of the claim could not be determined based on four points.

First Point: The Examiner points out that it is unclear from the claim as written where the reservoir means containing the vectors is located in relation to the delivery means and such that the vectors can in-fact be delivered to the cardiac tissue through the distal tip portion of the catheter.

Applicants have amended claim 20 to indicate that the reservoir means is located proximal to the said distal tip portion of said catheter. Support for this change was previously indicated. Applicants respectively indicate that the provided amendments of placing the reservoir proximal to the distal portion of said catheter makes the claim element definite under 35 U.S.C. Section 112, second paragraph.

Second Point: The Examiner found it unclear whether the Applicants intend the delivery means to 1) deliver the vector and 2) actively transfect or transduce the cardiac tissue with the vector or whether only the first step of delivering the vector was intended. The Examiner suggests that if Applicants intend the delivery device to

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conduction of the problematic cells or improves the cardiac conduction of normal cells surrounding the problematic cells. **[emphasis added]**

function solely to deliver the vector, it is suggested that the claim be amended to recite, "a delivery means for delivering a therapeutically effective amount of said recombinant nucleic acid vectors from said reservoir means through said distal tip portion of said catheter to said cardiac tissue **such that said cardiac tissue to transfected or transduced with said recombinant nucleic acid tissue. [sic]"**

Applicants have tried to understand the suggested change of the Examiner; however, it ultimately was unclear as what was actually being suggested. In order to move forward on the prosecution, Applicants have amended Claim 20 so that delivery of nucleic acid vector is tied to transfection or tranduction of the cardiac tissue. Applicants respectively suggest that the provided amendments of tying delivery of the vectors with transfecting or transducing the cardiac tissue, and ultimately expressing the vectors in the cardiac tissue makes the claim element definite under 35 U.S.C. Section 112, second paragraph.

Third Point: The Examiner points to the fact that the claim lacks antecedent basis for "said connexin proteins." Specifically, the claim refers to a conduction protein selected from the group Cx40, Cx43, and Cx45 without antecedent basis. Further, the Examiner points out that the claim as written lacks the step wherein the encoded protein are actually expressed in the cardiac tissue following transfection/transduction.

First, Applicants have amended Claim 20 to reference the term "recombinant nucleic acid vectors" throughout the claim, and have removed the reference to "said connexin proteins" that lacked antecedent bases. Second, to improve the clarity of the claim, Applicants have removed the reference to "a supply of recombinant nucleic acid vectors," and just use the term "recombinant nucleic acid vectors." Third, Applicants further submitted amendments to indicate that the cardiac tissue is

transfected or transduced with said recombinant nucleic acid vectors. Support for this change was previously indicated. This amendment in combination with the first claim element now indicates that recombinant nucleic acid vectors are selected from the group of vectors encoding a conduction protein selected from the group Cx40, Cx43, and Cx45 and further in combination with the last element they are expressed in the cardiac tissue. Support for these changes was also previously indicated.

Fourth Point: The claim appears to contain a typographical error. The claim misspells "transducing" as "transducting."

Applicants have corrected the indicated misspelling.

Conclusion: Applicants respectfully request reconsideration and withdrawal of the previous rejection of indefiniteness, and respectfully submit that Claim 20 is in condition to issue.

(2) Claims Rejections - 35 USC § 103

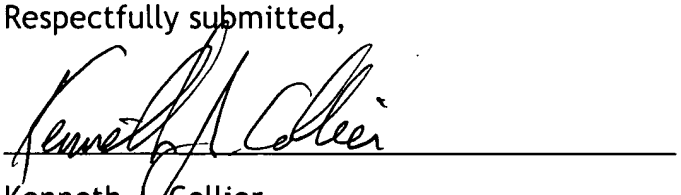
Previous claims 1, 4-9, 12-14, 24-25, and 39-42 had been rejected under 25 U.S.C. 103(a) over Mulier et al. in view of Leiden et al. and Kanter; however, this rejection was previously withdrawn in view of cancellation of these claims even though Applicants had included arguments that claim 20 was non-obvious over the art. Applicants appreciate the Examiner pointing out that the previous rejection is moot in view of the previous cancellation of claims.

Conclusion

Finally, Applicants would like to again thank Examiner Wehbe for her guidance in this application. Applicants would also like to thank Examiner Nguyen for faxing us copy of the Examination papers.

The enclosed response attempts to narrow the issues under consideration and to put Claim 20 in condition for allowance and the application be allowed to issue.

Respectfully submitted,



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